REMARKS

The invention includes a method for generating blood vessel in a mammal. The invention also includes a method for repairing or regenerating blood vessel in a mammal suffering from a disease, disorder or condition of the blood vessel or otherwise a vascular disorder.

As noted in the present Office Action Summary (PTOL-326), claims 55-77 are pending. Claims 55, 63 and 70 have been amended herein to indicate that the bone marrow stromal cells recited in these claims are culture expanded bone marrow stromal cells. Support for culture expanded cells is found throughout the specification, for example, on page 13, lines 3-14. Thus no new matter has been added by way of this amendment to the claims.

Priority

Applicants note that the claims have been indicated by the Examiner to have support in international application no. PCT/US96/04407, filed March 28, 1996. See present Office Action, page 2.

Applicants have amended the present claim for priority to correct a clerical defect in reciting that parent Application No. 08/913,918 was a national stage application and not a continuation under 35 U.S.C. § 111. As this corrects a clerical error, Applicants do not believe that a petition to change priority is required, as the grandparent PCT application was already claimed in the chain.

Claim Objections

The Examiner asserts that should claim 56 be found allowable, than claim 70 will be objected to under 37 C.F.R. 1.75 as being substantially duplicate thereof. Applicants respectfully submit that the objection will be address once claim 56 is deemed allowable.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 55-77 stand rejected as allegedly containing subject matter which lacks an enabling disclosure under 35 U.S.C. § 112, first paragraph. The Examiner contends that the specification is not enabling for methods of generating or repairing a blood vessel in a mammal, in a tissue specific manner or treating any disease, comprising administering bone marrow stromal cell to the mammal in need thereof. Rather, the Examiner asserts that the specification

merely discloses bone marrow stromal cells that are cultured from mice and the subsequent intravenous administration of the adherent cells obtained therefrom, to mice. Applicants respectfully submit that the claimed invention is enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

As an initial matter, Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. §112, unless there is a reason to doubt the objective truth of the specification. See, *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The initial burden of establishing a basis for denying patentability to a claimed invention rests upon the examiner. See, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984).

In addition, it is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

The law is also well-settled that extensive experimentation is not undue if one of ordinary skill in the art routinely engages in such experimentation. Further, the high degree of skill in the art, the extensiveness of experimentation routinely performed by the artisan, and that one skilled in the art of reference standards typically engaged in this type of experimentation at the time the application was filed must be considered. This is important, since the present case law regarding enablement under 35 U.S.C. §112, first paragraph, allows significant experimentation without finding it undue if the art typically engages in such experimentation.

The claims have been amended herein to encompass administration of culture

expanded bone marrow stromal cells and the development of these cells into cells of a blood vessel. Support for this amendment is found throughout the specification, for example in lines 8-10 on page 13, where the specification discloses that isolated stromal cells can develop into a blood vessel. Furthermore, beginning in line 30 on page 8, the specification discloses that isolated stromal cells, when administered to a mammal, can act as precursor cells which produce daughter cells that mature into differentiated cells. That is, the cells of the present invention can differentiate and develop into, but not limited to, cells of the blood vessels.

The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art. . . to make and/or use the invention." The Examiner provides an analysis of some of the *Wands* factors (*In re Wands*, 8 USPQ2d 1400). The *Wands* factors analyzed by the Examiner are reviewed below.

The Examiner states that the state of the art "teach the implantation and differentiation of marrow-derived mesenchymal stem cells for treatment of skeletal and other connective tissue disorders...and their engrafting in vivo". The Examiner concedes that the "art at the time of filing of the instant application is silent however, on the use of MSCs for differentiation into blood vessels and neovascularization...insight into the application of MSCs for the generation of blood vessels and angiogenesis may be obtained from the post-filing art..." In addition, the Examiner contends that the nature of the invention is not reasonably predictable given the lack of guidance in the specification, for the generation, repair or treatment of conditions requiring vascularization, following systemic or intraperitoneal administration of MSCs, and would require further and undue experimentation in view of the immaturity of the art.

Applicants believe that if the therapeutic result from administering MSCs into a mammal in need thereof embodies the state of the art, then such experimentation would appear to be routine and therefore not undue experimentation. As a second threshold issue, Applicants point out that a necessary element of the claimed invention is the appreciation for the ability of MSCs to form blood vessels or otherwise cells of the blood vessels. Thus, the practice of the invention does not require the determination or otherwise reduction to practice of the therapeutic result as predicted by the specification.

The Examiner's analysis of the state of the art at the time of filing of the present application demonstrates the considerable amount of literature disclosing the therapeutic potential of MSCs, particularly in treating disorders of the bone and cartilage (See Caplan et al. U.S. Patent No. 5,197,985 and Wilson et al. U.S. paten No. 5,817,773). However, the Examiner

neglects to mention that the prior art is silent on the ability of the transplanted MSCs to migrate following transplantation. That is, the prior art does not demonstrate that after intravenous injection into a mammal, the expanded cultures of adherent cells (e.g. bone marrow stromal cells) efficiently populated several connective tissues and also diffusely incorporated into the mesenchymal parenchyma of lung.

The cited prior art references demonstrate that the state of the art includes recognition that MSCs represented a small fraction of cells in bone marrow which can serve as stem-cell-like precursors of osteocytes, chondrocytes, and adipocytes. None of the references teach the aspect of MSCs forming blood vessels. This is confirmed by the Examiner in the present Office Action.

The Examiner cited the following post-filing references to demonstrate the unpredictability in the art with respect to MSCs generating blood vessels and angiogeneisis: Nagaya et al. (2004 Am J Physiol Heart Circ Physiol 287:H2670-H2676), Zisch et al., (2004 Curr Opin Biotech 15:424-429), and Dzau et al. (Hypertension 46:7-18).

With respect to Nagaya et al., the Examiner cites various statements to support the allegation that the art is immature. However, even though postdated references can be relied upon to show the level of skill in the art, Applicants point out that, it is impermissible to use a later factual reference to determine whether the application is enabled or described as required under 35 U.S.C. 112, first paragraph. *In re Koller*, 613 F.2d 819, 823 n. 5, 204 USPQ 702, 706 n.5 (CCPA 1980). In any event, the Examiner has taken the teachings of Nagaya out of context. The Examiner overlooks the major contribution of the article which demonstrates that intravenous administration of MSCs improved cardiac function after acute myocardial infarction through enhancement of angiogenesis and myogenesis in the ischemic myocardium (see abstract), partly due to the ability of MSCs to differentiate into vascular endothelial cells (see page H2675) or otherwise cells that make up blood vessels.

Furthermore, the Examiner notes that Nagaya cautions that "the limitation of this study is that the cell population may be mixed, rather than limited to MSCs". This statement is not applicable to the present invention. This is because the pending claims are directed to bone marrow stromal cells which are defined in the specification to refer to MSCs or adherent cells (population of cells isolated from bone marrow that adhere to plastic culture plates). As such, Nagaya actually demonstrates that MSCs, when intravenously administered, migrated to the

infracted myocardium and differentiated into at least vascular endotheilial cells or otherwise cells of the blood vessel.

With respect to Zisch et al., the Examiner equates endothelial progenitor cells (EPCs) with the cells of the present invention. Applicants point out that EPCs are not the same as MSCs. Therefore, it is inappropriate for the Examiner to rely on this reference to demonstrate the skill level in the art with respect to MSCs. Before any analysis of enablement can occur, it is necessary for the Examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition when examining the application, based on the Examiner's understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim. See *Genentech v. Wellcome Foundation,* 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994). Applicants submit that the claims are directed to bone marrow stromal cells and not to EPCs.

Further, the Examiner cites Dzau to expand upon the assertion that the art is immature. Similar to the inappropriateness of relying on Zisch, Dzau is equally directed to EPCs. As such, Applicants defer in making any arguments with respect to this reference at this time or at least until the Examiner has at least satisfied his initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Applicants submit that the Examiner has not satisfied the initial burden to establish a reasonable basis to question enablement. This is because two (Zisch et al. and Dzau et al.) out of the three references that the Examiner relies upon are not even directed to MSCs and that the one reference (Nagaya) actually appears to demonstrate post-filing reduction to practice of the claimed invention. This post-filing reference demonstrates that the invention has been further reduced to practice whereby the same methods as those included in the application were utilized to arrive at the results predicted in the as-filed application. These references provide evidence that the disclosure of the as-filed specification enables the claimed invention, and argues against the Examiner's assertion that the specification lacks enablement regarding the present invention.

In the present application, the claims at issue generally recite a method of generating a blood vessel in a mammal comprising administering culture expanded bone marrow stromal cells into the mammal in need thereof. The specification provides:

- a defined genus of cells (e.g. MSCs or bone marrow stromal cells or adherent cells) ;
- a description of the development of bone marrow stromal cells into cells of the blood vessels among other cell types; and
- a description of different modes of administering the cells of the invention into a mammal in need thereof.

Knowledge in the art included:

- knowledge and skill sufficient for isolating and culturing MSCs was routine in the art; and
- knowledge that MSCs can serve as stem cell-like precursors of osteocytes, chondrocytes, and adipocytes.

Where the art typically engages in a complex, but routine degree of experimentation, such activity, as a step in practicing the invention, is not undue experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning employed by the court in *In re Wands*.

Accordingly, Applicants respectfully submit that claims 55-77 are enabled, and request that the rejection of the claims under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn in view of the amendments and arguments set forth above.

Rejection of claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 under 35 U.S.C. § 102(b) as being anticipated by Boisvert et al. (1995 J Clin Invest 96:1118-1124). Specifically, the Examiner is of the opinion that Boisvert teaches a treatment for severe hypercholesterolemia in mice by transplantation of bone marrow from normal wild-type mice. Therefore, the Examiner asserts that Boisvert renders the broadest claim anticipated where the claim encompasses a method of administering bone marrow stromal cells to a mammal, wherein the cells differentiate into cell of the blood vessel anticipated. Applicants disagree for the following reasons.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is

contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). Therefore, Boisvert must describe each and every element of claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not satisfy this requirement.

Applicants respectfully assert that Boisvert cannot anticipate the present invention as encompassed in the pending claims because Boisvert teaches bone marrow transplantation, which is distinct from administering MSCs. At the time of filing the instant application, bone marrow transplantation was widely known in the field. However, the use of a subset cell population present in bone marrow (bone marrow stromal cells or MSCs) that are culture expanded for the formation of cells of the blood vessel was not known. The Examiner's citation of Boisvert is an example of a skill artisan practicing bone marrow transplantation. However, nowhere does Boisvert discuss the isolation of an adherent cell population from the bone marrow, culture expansion of these cells, and transplantation of the culture expanded MSCs to a mammal in need thereof for the formation of cells of the blood vessel.

Applicants submit that claims 55-56, 59-60, 63, 66-67, 70-71, and 74-75 are not anticipated by Boisvert et al. for the reasons set forth above, and request reconsideration and withdrawal of the rejection pursuant to 35 U.S.C. §102(b).

Rejection of claims 55, 58, 62-63, 65, 69-70, 73, and 77 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 55, 58, 62-63, 65, 69-70, 73, and 77 under 35 U.S.C. § 102(e) as being anticipated by Caplan et al. (U.S. Patent No. 5,197,985). Specifically, the Examiner is of the opinion that Caplan teaches methods of transplanting marrow-derived mesenchymal cells (otherwise MSCs, bone marrow stromal cells, adherent cells) into a mammal in need thereof. However, the Examiner concedes that Caplan does not teach the differentiation of administered stromal cells into cells of a blood vessel, which is consistent with the Examiner's statement of the "art at the time of filing of the instant application is silent however, on the use of MSCs for differentiation into blood vessels and neovascularization...insight into the application of MSCs for the generation of blood vessels and angiogenesis may be obtained from the post-filing art..."

According to the MPEP, an Office Action containing both a 35 U.S.C. § 112, first paragraph, enablement rejection and a prior art rejection under 35 U.S.C. § 102 and/or 103 against the same claim is not necessarily a contradiction or an improper Office action. However,

such a type of rejection should be limited to those art areas in which the teachings and suggestions in the art are in conflict with one another. The cited prior (Boisvert and Caplan) are not in conflict with each other. The Examiner concedes that Caplan does not teach differentiating MSCs into cells of the blood vessel and that Boisvert merely teaches bone marrow transplantation. Nowhere does Boisvert teach transplantation of culture expanded MSCs. Accordingly, these references cannot be in conflict with each other. As such, the present rejection is inconsistent with the examination policy set forth by the MPEP.

Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §102(e).

Rejection of claims 57-58, 61, 64-65, 68, 72-73 and 76 pursuant to 35 U.S.C. §103(a)

The Examiner has rejected claims 57-58, 61, 64-65, 68, 72-73 and 76 under 35 U.S.C. § 103(a) as being unpatentable over Boisvert et al. in view of Enright et al. (1995 Curr. Opin. Hematol. 2:293-299; abstract only provide by the Examiner). Specifically, the Examiner contends that Boisvert teaches a treatment for severe hypercholesterolemia in mice by systemic delivery and transplantation of allogeneic bone marrow from normal wild-type mice. Further, the Examiner asserts that systemic administration may be carried out either intravenously or intra-arterially. Therefore, the Examiner reasons that it would have been obvious for the skilled artisan to combine the methods of Boisvert with the methods for treating a human of Enright to arrive at the present invention. Applicants respectfully traverse this rejection for the following reasons.

As stated above, when an Office Action contains both a 35 U.S.C. § 112, first paragraph, enablement rejection and a prior art rejection under 35 U.S.C. § 102 and/or 103 against the same claims, the Examiner should make sure that such a type of rejection should be limited to those art areas in which the teachings and suggestions in the art are in conflict with one another. In any event, as discussed above, Boisvert does not teach MSCs let alone administration of culture expanded MSCs to a mammal. Rather, Boisvert teaches bone marrow transplantation in general.

The present invention encompasses the use of bone marrow stromal cells in the context of transplanting them into a mammal in need thereof to form cells of the blood vessels. Similar to Boisvert, Enright does not teach bone marrow stromal cells. Rather, Enright is a review article directed to marrow transplantation for the treatment of chronic myelogenous

leukemia. The marrow transplantation taught in this reference is directed to therapies for disorders or diseases of the hematopoietic system.

Applicants submit that Boisvert in view of Enright cannot render claims 57-58, 61, 64-65, 68, 72-73 and 76 *prima facie* obvious under 35 U.S.C. §103(a) following reasons. More specifically, the MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here because both references equally do not teach bone marrow stromal cells. In view of the lack of teaching of bone marrow stromal cells, Boisvert in view of Enright fails to offer a suggestion or motivation to modify the reference(s) to arrive at the instant invention. Furthermore, these references do not provide any reasonable expectation of success for using bone marrow stromal cells for the purpose of forming cells of the blood vessel. Similarly, these references do not teach or suggest all embodiments of the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

Double Patenting Rejection

Claims 55-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55-70 of co-pending application No. 10/423,232. Applicants respectfully request that the rejection be held in abeyance until claims are allowed in one of the two cases. Otherwise, addressing the rejection at this time would be considered premature.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that the claims are now in condition for allowance. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

DARWIN PROCKOP, ET AL.

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(Date)

By: _____

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